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September 26, 2003

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Steven L. Highlander

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: Serial Number 09/954,975 entitled "METHODS FOR TREATING HUMAN IMMUNODEFICIENCY VIRUS INFECTIONS WITH GALLIUM COMPOSITIONS" by Jack Stapleton et al.
Our ref: IOWA:033US / Matter No. 10108514

Commissioner:

Transmitted herewith for filing are:

1. Brief on Appeal (an original and two copies);

2. A check in the amount of $160.00 for the filing of Brief on Appeal); and

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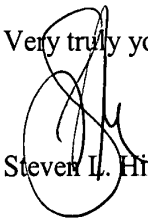

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Dr. Jack Stapleton
Dr. Bradley Britigan
Dr. Larry Schlesinger

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Jack STAPLETON *et al.*

Serial No.: 09/954,975

Filed: September 18, 2001

For: METHODS FOR TREATING HUMAN IMMUNODEFICIENCY VIRUS INFECTIONS WITH GALLIUM COMPOSITIONS

Group Art Unit: 1616

Examiner: F. Choi

Atty. Dkt. No.: IOWA:033US/SLH

BRIEF ON APPEAL

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Steven L. Highlander

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Examiner: F. Choi

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APPEAL BRIEF

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Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellant hereby submits an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences in response to the Final Office Action dated April 23, 2003. By virtue of the Notice of Appeal filed on July 23, 2003, this brief is due on September 28, 2003. The fee for filing this Appeal Brief is attached hereto. Should any other fees be due, or the attached fee be deficient or absent, the Commissioner is authorized to withdraw the appropriate fee from Fulbright & Jaworski Deposit Account No. 50-1212/IOWA:033US/SLH. Please date stamp and return the enclosed postcard to evidence receipt of this document.

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I. Real Party in Interest

The real party in interest is the assignee, University of Iowa Research Foundation, Iowa City, IA.

II. Related Appeals and Interferences

There are no interferences or appeals for related cases.

III. Status of the Claims

Claims 1-40 were filed with the original application. Claims 1-10 have been canceled. Claims 11-40 stand rejected. A copy of the rejected claims is attached as APPENDIX 1 to this brief.

IV. Status of Amendments

No amendments have been submitted following the final Office Action.

V. Summary of the Invention

In accordance with the present invention, there is provided a method of treating a human subject infected with human immunodeficiency virus (HIV) comprising administering to said subject an amount of a gallium composition effective to inhibit HIV replication. HIV may be HIV-1 or HIV-2. The gallium composition may be gallium nitrate, or may be a gallium-hydroxypyrone complex. The effective amount can be described as: achieving *in vivo* concentrations of about 1 to about 30 μM, or more specifically about 3 to about 20 μM. Alternatively, the effective amount is about 750 mg/m^2 given every two to three weeks, or about 100 to about 300 mg/m^2 per day. In one embodiment, the gallium composition is provided at levels sufficient to provide a blood plasma gallium concentration of 0.1 to 5.0 μg/ml. The gallium composition may be administered orally, for example, in the form of a tablet or a

capsule. Alternatively, the gallium composition is administered intravenously. Specification at page 4, line 25 to page 5, line 7.

In yet another embodiment, the method further comprises treating the subject with a second anti-viral agent in addition to the gallium composition, for example, a nucleoside analog that inhibits reverse transcriptase (NRTIs). Nucleoside analogs include dideoxyinosine, dideoxycytidine and 5-azidothymidine. Other anti-viral agents include protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Specification at page 5, lines 8-12.

In still yet another embodiment, there is provided a method of reducing virus shed from a human subject infected with HIV comprising administering to said subject an amount of a gallium composition effective to inhibit HIV replication. The method may also provide for reduced virus burden in a human subject infected with HIV, inhibition of loss of T cells in a human subject infected with HIV, increase in T cell numbers, in a human subject infected with HIV, or inhibition of development of acquired immunodeficiency syndrome in a human subject infected with HIV. Specification at page 5, lines 13-19.

In still a further embodiment, there is provided a therapeutic composition comprising (a) a gallium composition; and (b) a nucleoside inhibitor. The gallium composition may be gallium nitrate, or may be a gallium-hydroxypyrone complex. The NTRI may be one or more of the compounds selected from the group of didexoyinosine, dideoxycytidine and 5-azidothymidine. Also provided is a kit comprising, in suitable container means (a) a gallium composition; and (b) a nucleoside reverse transcriptase inhibitor. Specification at page 5, lines 20-26.

VI. Issues on Appeal

Are claims 11-13 and 16-40 obvious over U.S. Patent 5,093,134 ("the '134 patent"; Exhibit A) and Narasimhan *et al.* ("Narasimhan"; Exhibit B)?

Are claims 11-40 obvious over Narasimhan, U.S. Patent 5,525,598 ("the '598 patent"; Exhibit C) and U.S. Patent 5,883,088 ("the '088 patent"; Exhibit D)?

VII. Grouping of the Claims

The claims do not stand and fall together, as discussed in §IX.C, below.

VIII. Summary of the Argument

The present rejections, though using different combinations of references, are both based on the same flawed premise – that the knowledge of gallium inhibition of ribonucleotide reductase, can render its use as an HIV therapeutic obvious. The secondary references, some of which teach the inclusion of gallium in the context of more complex compositions, certainly do not render the use of gallium *per se* obvious since ***none of them teach or suggest that there would be any therapeutic benefit in treating HIV-infected patients with gallium***. In sum, the rejection is based on a hindsight reconstruction of the invention, using appellants' disclosure as a road map. At best, the art presents an obvious to try scenario would ***not*** be the proper basis for rejection.

IX. Argument

A. Rejection Under §103 over the '134 Patent and Narasimhan

Claims 1-4, 7-13 and 16-40 are rejected under 35 U.S.C. §103(a) as allegedly obvious over the '134 patent in view of Narasimhan. The '134 patent is cited as teaching the use of gallium complexes to treat HIV. Narasimhan is cited as teaching that gallium inhibits ribonucleotide reductase. The examiner also relies on the facts (a) T lymphocytes are lost when infected with HIV, and (b) ribonucleotide reductase inhibitors are currently used in combination therapies for HIV. While the examiner acknowledges that the prior art fails to disclose a method

of treating HIV with gallium, it is argued that "the prior art amply suggests the same as it is know that compositions containing gallium are effect against HIV and ... [that] gallium is a ribonucleotide reductase inhibitor and that ribonucleotide reductase inhibitors potentiate the effects of dideoxynucleotides." Appellants traverse.

As with every obviousness analysis, it is of critical importance that one not lose sight of the requirements for a valid *prima facie* case. Those requirements are aptly spelled out in *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed Cir. 1991). In that case, the Federal Circuit stated that in order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. See also *Manual of Patent Examining Procedure* §2142.

It is not disputed that Narasimhan discloses that gallium inhibits ribonucleotide reductase. In addition, it is also worth noting that gallium nitrate was shown to inhibit reverse transcriptase as early as 1974. See the '598 patent, col. 1, lines 28-32. However, one cannot overlook the fact that Narasimhan fails to mention anything regarding anti-viral applications, much less about HIV therapy. Thus, motivation to use gallium as an anti-HIV therapeutic must come from somewhere else.

On the other hand, the '134 patent clearly addresses HIV therapies:

> We have now discovered certain polyoxometallate compounds which exhibit not only activity against HIV in the screening tests used, but also relatively low toxicity against cells. Accordingly, the present invention provides as active compound for the various aspects of the invention, a compound selected from those containing ions of the Keggin structure, an defined by the general formula:

$A_x[MDLW_{11}]_{39}.yH_20$ (I)
$A_x[D'(MW_{11}O_{39})_2].yH_20$ (Ia)

...
D is a metal and D' is a lanthanide in oxidation state 3 or 4,
....

Col. 2, lines 18-37. Moreover, the ***only explicit mention*** of gallium in the entire '134 patent is at col. 3, where gallium is listed as one of ***ten possible metal ions***, and in Table (columns ¾), where two gallium-containing compounds were tested (out of 15 other compounds "according to the invention"). Appellants respectfully submit that one of skill in the art, reading this document, would find ***nothing*** to suggest that ***gallium itself acts as an antiviral agent***. To the contrary, gallium appears to be nothing more than one of a variety of non-critical metal ions that are inconsequential to the activity of the overall compounds.

Now, returning to the *Vaeck* factors set out above, appellants submit that the examiner has not identified, ***in the prior art***, the appropriate motivation to select gallium as a primary therapeutic agent. *In re Soli*, 137 U.S.P.Q. 797 (CCPA 1963). All the cited art teaches is (a) a biological activity of gallium with no mention of utility, and (b) anti-viral compositions which happen to optionally include gallium. The examiner has, in this situation, apparently used appellants' own disclosure to provide the motivation, which is improper. *In re Carroll*, 202 U.S.P.Q. 571 (CCPA 1979) ("One of the more difficult aspects of resolving questions of non-obviousness is the necessity 'to guard against slipping into the use of hindsight"). Though some "hindsight" is required in order to properly search the invention, once the most relevant art has been identified, the examiner must establish that the requisite motivation exists ***in the cited art***. As above explained, the art fails in this regard.

It also is worth stating that the prior art says nothing about the ability of gallium, as a therapeutic agent, to inhibit HIV. While the compounds of the '134 patent were shown to have *in vitro* effects, these were not gallium *per se*, but compounds that contained gallium ***in the context of polyoxymetallates***. As such, this reference says little, if anything, regarding the efficacy of gallium to treat HIV. Narasimhan is notably silent on treatments, and cannot therefore provide any meaningful comment on the issue of likelihood of success.

The examiner's rebuttal to this line of argument is not helpful. First, it is argued that appellants "cannot show nonobviousness by attacking references individually." This truism is not a very productive, or even worthwhile observation – in fact, how does one attack more than one reference at a time? In reality, ***every rebuttal by definition will address the references individually***. Thus, the legal citations to *Keller* and *Merck* simply avoid the issue. Surely the examiner will agree that motivation is a necessary requirement for obviousness, so again, the question becomes ***where does the motivation derive from to use gallium in an HIV therapy***? Yet as stated above, the '134 patent clearly cannot be read as providing ***any*** suggestion to use gallium in HIV therapy. Narasimhan, which would appear to have the most relevance here, does not even ***hint*** at therapeutic endeavors. Thus, the impropriety of the rejection remains evident.

Next, the examiner states that "the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference ...." This quotation is quite perplexing, since appellants have argued nothing of the sort. To the contrary, it would appear quite simple, to combine gallium with an anti-HIV pharmaceutical. On the other, hand it remains quite true that the reference do not suggest using gallium as an HIV therapeutic - expressly, implicitly or otherwise - and that is the downfall of the examiner's position. No quantum of legal citations makes up for this deficiency.

Moreover, the examiner has not even attempted to address likelihood of success in inhibiting HIV *in vivo*. Admittedly, Narasimhan does not address HIV replication and infection *in vivo*. Thus, on the record, this is insufficient evidence to even begin to address whether gallium can inhibit HIV in a human subject. At best, this presents an "obvious to try" situation, which the Federal Circuit has emphasized is not proper. In particular, one cannot find obviousness where the prior art provides only "a ... general approach that seemed to be a promising field of experimentation, where ... gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Precisely such a case is presented here.

In conclusion, appellants respectfully submit that the references, even when viewed in combination, fail to appropriately suggest that one could use gallium as an anti-HIV therapy, much less use it successfully. As such, appellants respectfully submit that the rejection is founded on an improper obviousness analysis, and thus a *prima facie* case has not been established. Reversal of the rejection is therefore requested.

B. Rejection Under §103 over Narasimhan, and the '598 and 088 Patents

Claims 1-40 stand rejected under §103 as allegedly obvious over Narasimhan, the '598 patent and the '088 patent. Narasimhan is cited as above. The '088 patent, as implicitly acknowledged, only deals with gallium formulations and says nothing about HIV. Thus, the critical reference here is the '598 patent, which is cited by the examiner as teaching that "gallium complexes are effective at treating HIV and that gallium nitrate inhibits reverse transcriptase found in retroviruses, such as HIV." While the examiner acknowledges that the prior art fails to disclose a method of treating HIV with gallium, it is argued that "the prior art amply suggests the

same as it is know that compositions containing gallium are effect against HIV and ... [that] gallium is a ribonucleotide reductase inhibitor and that ribonucleotide reductase inhibitors potentiate the effects of dideoxynucleotides." Appellants traverse.

This rejection is very similar to that advanced above with two exceptions: (a) Narasimhan is used as the primary reference here, and (b) the '088 patent is cited to support rejection of certain dependent claims. Otherwise, the reasoning appears to be precisely the same. That said, appellants again point out that, despite the teachings of Narasimhan, that reference fails to mention anything regarding anti-viral applications, much less about HIV therapy. Thus, motivation to use gallium as an anti-HIV therapeutic must come from somewhere else.

The '598 patent, on the other hand, very clearly describes the possibility of HIV therapies: "It has now been found that certain gallium (III) complexes have antitumor and antiviral activities. The invention gallium (III) complexes comprise gallium (III) complexes of N-heterocycles." Col. 1, lines 39-43. Thus, far from focusing on gallium, the '598 patent discusses a complex heterocyclic compound that contains, as one aspect, gallium (III) ions. Moreover, there is only marginal information in the '598 patent on the activity of these compounds, and what information there is suggests that these compounds are far less effective at inhibiting HIV (low EC_{50}/IC_{50} ratio) than existing drugs such as AZT. Notably, the issued claims in the '598 patent ***are limited to use of these compounds to treating tumors***. Appellants respectfully submit that one of skill in the art, reading this document, would find very little to suggest that ***gallium itself acts as an antiviral agent*** without being part of a more complex compound, and in fact, ***one would doubt its efficacy even in that environment***.

Now, returning to the *Vaeck* factors set out above, appellants submit that the examiner has not identified, ***in the prior art***, the appropriate motivation to select gallium as a primary

therapeutic agent. *In re Soli, supra.* All the cited art teaches is (a) a biological activity of gallium with no mention of utility, and (b) compositions which include gallium in the context of a N-heterocycles, which themselves have dubious antiviral properties. The examiner has, again, apparently used appellants' own disclosure to provide the motivation, which is improper. *In re Carroll, supra.* Though some "hindsight" is required in order to properly search the invention, once the most relevant art has been identified, the examiner must establish that the requisite motivation exists ***in the cited art.*** As above explained, the art fails in this regard.

It also is worth stating that the prior art does not provide sufficient information regarding the ability of gallium to act as a therapeutic agent against HIV. While the compounds of the '598 patent were shown to have marginal *in vitro* effects, these were not gallium *per se*, but compounds that contained gallium ***in the context of N-heterocycles***. As such, this reference says little, if anything, regarding the efficacy of gallium (or even gallium-containing N-heterocycles) to treat HIV. Narasimhan is notably silent on treatments, and cannot therefore provide any meaningful comment on the issue of likelihood of success.

The examiner offers absolutely nothing in response to this rebuttal other than to refer to the same off point case cites discussed above. Thus, it remains appellants' position that a *prima facie* case has not been established as the references do not clearly identify gallium itself as an HIV therapeutic, nor do they establish, with any reasonable probability, that if given to an HIV-infected subject, that it would have any beneficial effects *in vivo*. As such, and in light of the controlling case law, the rejection is improper. Reversal of the rejection is therefore requested.

C. Separate Patentability

There are a number of claims that stand separately patentable over claim 11, upon which much of the rejection is focused. For example, whatever might be gleaned from the references

regarding "treatment" generally, they do not even begin to address the specific recitations of reducing virus shed (claim 31), reducing virus burden (claim 32), and inhibiting development of AIDS (claim 34). The failure of the examiner to even address these distinct embodiments precludes a finding of obviousness.

X. Conclusion

It is respectfully submitted, in light of the above, that all claims are non-obvious. Therefore, appellants request that the Board overturn each of the pending grounds for rejection.

Respectfully submitted,

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Date: September 26, 2003